

Short
reportTherapy for genital herpes in
immunocompromised patients: a national survey

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Objectives: To estimate the extent of aciclovir refractory herpes simplex virus (HSV) infection in HIV coinfecting patients in the United Kingdom and survey clinicians on their approaches to its management.

Design: Questionnaire survey of representative sample of one third of United Kingdom HIV physicians.

Main outcome measures: Use of antiviral therapies for genital HSV infections in HIV positive patients, reported frequency of aciclovir refractory HSV infection, its therapy, and access to antiviral susceptibility testing facilities.

Results: 53 responses were obtained (response rate 61%), representing a sample size of 23% of United Kingdom HIV physicians. Use of non-standard antiviral regimens for HSV infections in HIV coinfecting patients was widely practised, irrespective of the clinical characteristics of the HSV infection. Aciclovir refractory HSV infection has been observed by 37 (70%) respondents. Although foscarnet was the most frequently used therapy, used by 27/37 (73%) respondents, in only seven of these 27 (19%) was it a first line treatment for aciclovir refractory cases, frequently being used at a late stage in the clinical course. Antiviral susceptibility testing facilities were available to 46 (87%) clinicians. No respondents reported any evidence of transmission of aciclovir resistant strains.

Conclusions: HIV coinfection has a stronger influence on therapeutic choice than clinical immunosuppression or severity of herpetic infection. Aciclovir treatment failure is commoner than hitherto recognised. There is a need for wider awareness of use of foscarnet at an earlier stage in management of refractory HSV infection.

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Keywords: herpes simplex virus; genital herpes; immunocompetence

Introduction

Herpes simplex virus (HSV) disease is a major cause of morbidity in immunocompromised individuals, with a greater frequency, severity, and chronicity which is proportionate to the degree of immunosuppression.^{1,2}

Chronic HSV ulceration which is clinically refractory to standard doses of aciclovir and associated with *in vitro* resistance has been widely reported in association with both HIV and other causes of immunosuppression.²⁻¹¹ In HIV positive patients, most refractory HSV infections occur when the CD4 count is below $100 \times 10^6/l$.

Management of aciclovir refractory HSV disease in AIDS patients has been widely discussed; therapeutic options include intravenous aciclovir, foscarnet, vidarabine, trifluorothymidine, and cidofovir.⁵⁻¹⁰ A recent consensus conference summarised current evidence and recommended treatment guidelines for resistant HSV disease.⁹

Despite numerous case reports in the literature, firm quantitative information is currently lacking on the extent of aciclovir refractory HSV disease in clinical practice. This survey aimed to investigate current approaches to management of HSV infections in HIV positive patients, the extent of aciclovir treatment failure in United Kingdom practice, the range of therapies used by clinicians in its management, and availability of antiviral sensitivity testing facilities to HIV physicians.

Methods

The National AIDS Manual is a regularly updated compendium of HIV treatment centres in the United Kingdom. Of 231 HIV consultants listed in the 1994 manual, a representative sample of 87 individuals was selected, ensuring inclusion of all major treatment centres in the United Kingdom; 40 (46%) were in Greater London and 47 (57%) in the remainder of the United Kingdom. A questionnaire was sent to the consultants, with questions relating to the following areas:

(a) Use of antiviral therapies in HIV positive patients.

(b) Experience of HSV infection refractory to aciclovir (defined as failure of culture proved HSV infection to resolve after 2 weeks of continuous oral aciclovir therapy in conventional doses).

(c) Access to antiviral susceptibility testing facilities.

After a period of 6 months, a second questionnaire was sent to non-responders.

Results

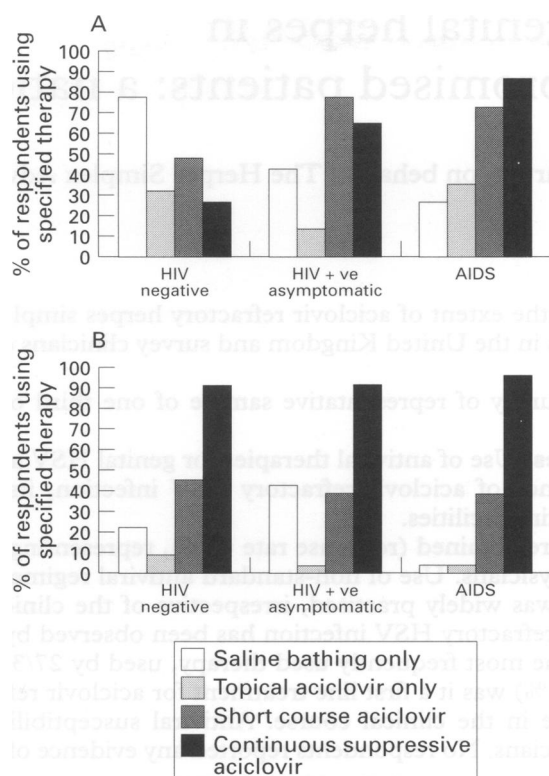
In all, 53 consultants responded, an overall response rate of 61%, representing a sample size of approximately 23% of United Kingdom HIV consultants.

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Scenario (A): two mild episodes per year, each lasting 4 days. (Percentage of respondents who "always" or "frequently" use therapy specified.) Scenario (B): nine severe episodes per year, each lasting 8–10 days (percentage of respondents who "always" or "frequently" use therapy specified).

USE OF ACICLOVIR

Initial episodes of genital herpes in HIV positive patients

- Same initial approach as in HIV negative patient, 27 (51%)
- Always use a different approach, seven (8%)
- Use a different approach in selected patients, 17 (31%). Differences in therapeutic approach included changed dosage, duration, or both. Stated selection criteria for using a different approach included various CD4 count thresholds between 100 and 500, "immunosuppression", appearance or number of herpetic lesions.

Table 1 Experience of aciclovir refractory HSV infection

	HIV caseload > 50 patients	HIV caseload ≤ 50 patients
Total number of respondents	31	20
No (%) reporting aciclovir refractory HSV cases	26 (84)	11 (55)
No of aciclovir refractory cases seen in past 5 years	113	33
Total no of aciclovir refractory cases seen	215	33
Mean (range) per respondent	8.6 (1–30)	4.1 (1–10)

Table 2 Therapy used in aciclovir refractory HSV infection

	Ever used	Only therapy specified
Increased oral dose of aciclovir	23	3
Intravenous aciclovir	17	2
Famciclovir	2	1
Foscarnet	27	7
Trifluorothymidine	9	0

RECURRENT EPISODES OF GENITAL HERPES

Two scenarios were postulated, one described patients with two mild episodes per year, each lasting 4 days and the other described nine severe episodes per year, each lasting 8–10 days. The figure shows the treatment approaches which respondents commonly used in patients with varying degrees of immunosuppression.

EXPERIENCE OF ACICLOVIR REFRACTORY

HERPES SIMPLEX INFECTIONS (TABLE 1)

Aciclovir refractory herpes simplex infections had been observed by 37 (70%) of the 53 respondents. This experience was commoner in respondents with higher HIV caseloads—being reported by 26 (84%) of the 31 respondents with a caseload of 50 or more but only by 11 (55%) of those with fewer than 50 patients. Thirty two respondents stated that all such patients had AIDS, but five reported aciclovir refractory HSV infection occurring in other clinical situations, including two cases in HIV negative individuals (one patient with chronic lymphocytic leukaemia and one idiopathic case).

THERAPY USED IN ACICLOVIR REFRACTORY HSV INFECTION (TABLE 2)

Altogether, 13 respondents had used only one therapy in this situation, but the remaining 24 had used several. Foscarnet was more frequently used by experienced HIV clinicians with current caseloads of more than 50 patients (84% compared with 69% of clinicians with caseloads of 50 or less). All seven respondents who indicated that foscarnet was the only treatment used had a caseload of more than 50 patients.

THERAPY USED SUCCESSFULLY IN ACICLOVIR REFRACTORY HSV INFECTION

Twenty respondents had found only one therapy to be successful; 11 (55%) stated this to be foscarnet. The remaining 17 respondents had used several different therapies. Four respondents reported that they had found no successful treatment, of whom two had never used foscarnet and the other two reported use of foscarnet as a third line treatment.

After resolution of previously refractory HSV lesions, 20 respondents were able to recommence oral therapy with either aciclovir or famciclovir, but eight stated that continuation of foscarnet was required.

ACCESS TO ANTIVIRAL SUSCEPTIBILITY TESTING FACILITIES

One respondent indicated that all isolates were routinely tested for aciclovir sensitivity; 45 had the facility available if resistance is clinically suspected. The remaining seven respondents were unsure about the availability of this service at their centre.

EVIDENCE FOR TRANSMISSION OF ACICLOVIR RESISTANT VARIANTS OF HSV

In all, 36 of the 37 respondents who reported aciclovir refractory HSV stated that there was no clinical evidence of transmission between

partners. One respondent left this question blank.

Conclusions

This survey investigated issues surrounding aciclovir resistant HSV in HIV infected individuals, with specific emphasis on its frequency in clinical practice and current approaches to therapy.

HSV isolates from mucocutaneous lesions in both immunocompetent and immunosuppressed populations contain a mixed population of strains, up to 7% of which show reduced susceptibility to aciclovir.¹⁰ Although the recovery of resistant isolates from immunocompetent hosts has not been associated with clinical disease, reports of antiviral resistance have now become commonplace in the context of HIV infection.²⁻¹¹ The spontaneous mutation rate to resistant phenotypes is estimated at 1 in 100 000; immunosuppression facilitates higher HSV replication rates, which may allow resistant mutants to resist host defences and eventually predominate within the lesion. In vitro aciclovir resistance in HSV isolates from HIV positive patients is highly predictive of aciclovir treatment failure.⁴

The survey highlighted a number of issues concerning antiviral therapy for HSV disease. An HIV diagnosis per se has a stronger influence than severity of HSV disease on the likelihood of a patient receiving aciclovir therapy. Treatment thresholds for HIV positive individuals are low. Despite lack of evidence to support its use, a high proportion of clinicians use more prolonged aciclovir therapy for mild herpetic disease in patients who are HIV coinfectd. This is a matter for concern, given that prolonged exposure to antiviral drugs is associated with detection of resistant variants.^{2,4,10}

Clinical experience of aciclovir refractory HSV disease is widespread in United Kingdom HIV physicians; 70% of this representative sample had managed this problem. However, therapy for this condition showed inconsistency. Although foscarnet was the most frequently used therapy, selected by 27/37 (73%) respondents, in only seven of these 27 cases (19%) was it a first line treatment for aciclovir refractory HSV. Although there is now good evidence to support early use of foscarnet as first line therapy for aciclovir resistant disease,^{5,6,9} 65% of respondents use the drug at a late stage in the clinical course, after unsuccessful trial of several other agents. This feature was less marked among respondents with higher caseloads and experience of treating more cases of aciclovir refractory HSV disease. Although there have been sporadic anecdotal reports of resistance to fos-

carnet,^{8,11} this has not to date been recognised as a substantial problem. Use of foscarnet at an earlier stage should therefore be encouraged in improving outcomes within this area of clinical practice.

Antiviral susceptibility testing facilities were available to 46 (87%) clinicians. No respondents reported any evidence of transmission of aciclovir resistant strains between partners. Opportunities for improving recognition and management of aciclovir refractory HSV infection should be sought, particularly given the survey's finding that the problem may be commoner than previously recognised.

The herpes simplex advisory panel

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